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(54) **Title:** METHODS, SYSTEMS, AND COMPOSITIONS FOR TREATING OR AMELIORATING THE EFFECTS OF A NON-CONGENITAL HYPERTONIA

(57) **Abstract:** The present invention relates to methods, systems, and compositions for treating or ameliorating the effects of a non-congenital hypertonia. In particular, a method is provided for treating or ameliorating the effects of a non-congenital hypertonia in a patient. This method includes administering to a patient an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites or pharmaceutically acceptable salts thereof.

# METHODS, SYSTEMS, AND COMPOSITIONS FOR TREATING OR AMELIORATING THE EFFECTS OF A NON-CONGENITAL HYPERTONIA

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** The present application claims benefit to U.S. provisional patent application no. 60/926,601 filed on April 26, 2007, which is incorporated by reference in its entirety as if recited in full herein.

## FIELD OF THE INVENTION

**[0002]** The field of the present invention relates to methods, systems, and compositions for treating or ameliorating the effects of a non-congenital hypertonia.

## BACKGROUND OF THE INVENTION

**[0003]** Hypertonia is the disabling increased muscle tone disorder that often follows brain injury such as stroke, head trauma, and other central nervous system injuries. There are millions of people world-wide who are afflicted with hypertonia of various etiologies.

**[0004]** For example, there are about 750,000 new strokes per year in the US. The prevalence of patients living with chronic stroke was about 4.7 million in 2003. Approximately 60-80% (3.8 million) of stroke patients have a motor deficit. Post-stroke hypertonia seriously hinders rehabilitation of hemiparesis. From a recent study of consecutive stroke patients with hemiparesis, 63% developed hypertonia during the 6 months after stroke. This means that up to about 2.4 million patients may benefit from improved treatments of this disease.

**[0005]** There are a number of treatment protocols available to patients suffering from, e.g., post-stroke hypertonia. These treatment protocols include use of various drugs, including baclofen (Lioresal), tizanidine (Zanaflex), trihexylphenidate (Artane), clonazepam (Klonipin) diazepam (Valium), and botulinum toxin. All of the forgoing treatment protocols, however, suffer from one or more drawbacks: somnolence, tolerance, ataxia, respiratory and cardiac depression (baclofen); dry mouth, somnolence, and dizziness (tizanidine); dry mouth, blurred vision, and dizziness (trihexylphenidate); sedation and tolerance (clonazepam); and swallowing problems, voice changes, dry mouth, droopy or swollen eyelids, double vision, dry eyes, and tearing (Botox).

**[0006]** Thus, there is a need for methods and compositions for treating hemiparesis caused by a non-congenital hypertonia, which do not suffer from the drawbacks identified above.

## SUMMARY OF THE INVENTION

**[0007]** The present invention is directed to meeting the foregoing and other needs. In this regard, one embodiment of the invention is a method for treating or ameliorating the effects of a non-congenital hypertonia in a patient. This method comprises administering to the patient an effective amount of a non-sedative, long-acting γ-aminobutyric acid receptor subtype A ($GABA_A$) agonist or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

**[0008]** Another embodiment of the invention is a pharmaceutical composition for treating or ameliorating the effects of a non-congenital hypertonia in a patient

comprising a pharmaceutically acceptable carrier and an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

**[0009]** A further embodiment of the present invention is a method for rehabilitating hemiparesis caused by post-stroke hypertonia. This method comprises (a) administering to a patient suffering from hemiparesis caused by post-stroke hypertonia an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof and (b) treating the patient with a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

**[0010]** Yet another embodiment of the invention is a system for improving the clinical outcome of a patient suffering from hemiparesis caused by a non-congenital hypertonia comprising: (a) prescribing, administering, or causing to be administered to a patient suffering from hemiparesis caused by a non-congenital hypertonia an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof and (b) further prescribing, administering, or causing to be administered to the patient a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

**[0011]** Another embodiment of the invention is a method for identifying a patient suffering from hemiparesis caused by a non-congenital hypertonia, which patient will benefit from treatment with a non-sedative, long-acting 1,5-benzodiazepine. This method comprises: (a) performing a first motor function test on a patient suffering from hemiparesis caused by a non-congenital hypertonia; (b) administering a fast-acting 1,5-benzodiazepine to the patient after completion of the first motor function test; (c) administering to the patient a second motor function test, which is identical to the first motor function test, while the patient is under the influence of the fast-acting 1,5-benzodiazepine; and (d) determining whether the patient's performance improved in the second motor function test compared to the first motor function test, wherein an improved performance in the second motor function test is indicative that the patient will benefit from treatment with a non-sedative, long-acting 1,5-benzodiazepine.

**[0012]** A further embodiment of the invention is a method for rehabilitating hemiparesis caused by post-stroke hypertonia. This method comprises: (a) prescribing, administering, or causing to be administered to a patient suffering from hemiparesis caused by post-stroke hypertonia between about 10 mg/day to about 20 mg/day of clobazam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof and (b) prescribing, administering, or causing to be administered to the patient a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

## DETAILED DESCRIPTION OF THE INVENTION

**[0013]** The emergence of post-stroke dystonia may represent a maladaptive reorganization of inhibition-excitation balance. In view of the foregoing observation and not wishing to be bound by a particular theory, it is believed that a GABA challenge may reduce excessive excitatory influence in the stroke hemisphere and mediate a more normal corticospinal output. The present invention is directed to new treatment approaches for this difficult condition.

**[0014]** Thus, one embodiment of the present invention is a method for treating or ameliorating the effects of a non-congenital hypertonia in a patient comprising administering to a patient an effective amount of a non-sedative, long-acting γ-aminobutyric acid receptor agonist or a 1,5-benzodiazepine (*e.g.* clobazam) or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites or pharmaceutically acceptable salts thereof.

**[0015]** In the present invention, a hypertonia is marked by an abnormal increase in the tightness (tension) of muscle tone and a reduced ability of a muscle to stretch (i.e., increased stiffness). Damage to, e.g., upper motor neurons may cause such a hypertonia, as well as, spasticity and rigidity. Untreated, hypertonia may lead to loss of function and deformity of, e.g., limbs.

**[0016]** The causes of hypertonia are varied and may include, e.g., disease or brain injury. In the present invention, the hypertonia is not congenital (i.e., it is non-congenital). Particular examples of causes of non-congenital hypertonia within the scope of the present invention include, e.g., stroke, head trauma, brain tumor, post-surgical injury, cerebral palsy, and primary and secondary dystonias.

**[0017]** As used in the present invention, "dystonia" means a persistent and prolonged co-contraction of both the agonist and antagonist muscles resulting in abnormal posturing (over flexion, over extension, rotation) at rest and/or duration of action. (See, e.g., J. Jankovic, Dystonia: medical therapy and botulinum toxin. *Adv. Neurol* 94:275-286 (2004). Table 1 below exemplifies common non-congenital (i.e., acquired) dystonias.

**Table 1 - Summary of Clinical Characteristics (n=33)**

| | Age of onset (mean) | Latency (mean) | Site of onset (% of cases) | Lesion site (% of cases) |
|---|---|---|---|---|
| **Post stroke (n=10)** | 2-69 yrs (40.5) | 3 mos- 3 yrs (9.5 mos) | Arms: 5/10 (50)<br>Legs: 2/10 (20)<br>Both: 3/10 (30) | 5 basal ganglia (55)<br>3 thalamus (33)<br>3 cortical (33) |
| **Post trauma (n=8)** | 5-39 yrs (16.4) | 2 weeks - 10 yrs (27.5 mos) | Arms: 5/8 (62.5)<br>Both: 3/8 (37.5) | 2 basal ganglia (50)<br>1 cortical (25)<br>1 subcortical<br>1 midbrain (25) |
| **Perinatal (n=9)** | 1-17 yrs (9.7) | 1-17 yrs (9.7) | Arms: 3/9 (33)<br>Legs: 3/9 (33)<br>Both: 3/9 (11) | 3 basal ganglia (42)<br>1 thalamus (14.3)<br>2 cortical (28)<br>1 cerebellum/pons (14.3) |
| **Miscellaneous (n=6)** | 5 mos. - 16 yrs (6.3 yr) | 1-9 mos (4.5 mos) | Arms: 3/6 (50)<br>Legs: 1/6 (16.6)<br>Both: 2/6 (33) | 2 basal ganglia (40)<br>3 thalamus (60)<br>2 cortical (40) |

**C. Chuang *et al.*, JNNP 72:59-67 (2002)**

**[0018]** As used herein, "spasticity" means a velocity-dependent increase in the tonic stretch reflexes (muscle tone) and exaggerated tendon jerks resulting from hyperexcitability. (See, e.g., JW Lance, Physiology of spasticity. In Spasticity: Disordered motor control year book (Chicago 1980)).

**[0019]** In the present invention, the hypertonias, including dystonia, spasticity, and combinations thereof may be treated with a non-sedative, long-acting γ-aminobutyric acid receptor subtype A ($GABA_A$) agonist, such as a 1,5-benzodiazepine, e.g., clobazam. Clobazam is commercially available and is known by a variety of tradenames, including, e.g., Chlorepin, Clorepin, Frisium, Mystan, Urbadan, and Urbanyl. Clobazam was first synthesized in 1969 and its synthesis is well known. See, e.g., Giunta F. et al., Boll Soc Ital Biol Sper. 1969 Nov 30;45(22):1473-5 and Kuch, H. Br J Clin Pharmacol. 1979;7 Suppl 1:17S-21S, which are incorporated by reference as if recited in full herein.

**[0020]** Clobazam is a 1,5-benzodiazepine with the chemical name of 10-chloro-6-methyl-2-phenyl-2,6-diazabicyclo[5.4.0]undeca-8,10,12-triene-3,5-dione. Clobazam is an agonist for the inhibitory neurotransmitter $GABA_A$ (Cl-channel) receptor. Clobazam has less affinity for the $\omega_1$ GABA receptor binding site, which is the site associated with the sedating properties of the 1,4-benzodiazepines, such as diazepam. Indeed, clobazam has been shown to be much less sedating than either 0.5 mg or 1.0 mg of clonazepam. (See, e.g., JD Wilden et al., *Br J. Clin Pharm* 29:169-77 (1990)).

**[0021]** In the present invention, a compound or composition is "non-sedative" if its administration to a patient does not sedate the patient. Preferably, a non-sedative compound or composition does not render the patient drowsy. More

preferably, a non-sedative compound or composition has the same or better side-effects, viz sedation, as clobazam.

**[0022]** In the present invention, an "effective amount" or "therapeutically effective amount" of a γ-aminobutyric acid receptor agonist or a 1,5-benzodiazepine, such as for example clobazam, is that amount of such compound and/or composition that is sufficient to effect beneficial or desired results as described herein. In terms of treatment of a mammal, *e.g.*, a human patient, an "effective amount" is an amount sufficient to treat, reduce, manage, palliate, ameliorate, or stabilize a condition, such as a non-congenital hypertonia that is characterized by dystonia, spasticity, or both, so that a routine of physical therapy, occupational therapy, speech therapy, or combinations thereof provide, e.g., improved tone, improved power, improved flexion, improved extension at a joint, improved muscle control, improved gait, improved speech, improved motor control, improved coordination, and combinations thereof in the patient compared to carrying out the routine in the absence of the compound or composition. Thus, as used herein, "carried over to the patient's personal environment" means that through the sustained action of a γ-aminobutyric acid receptor agonist or a 1,5-benzodiazepine, such as for example clobazam, improved tone, improved power, improved flexion, improved extension at a joint, improved muscle control, improved gait, improved speech, improved motor control, improved coordination, and the like, including combinations thereof are enjoyed by the patient in his or her daily life outside of the confines of a physical, occupational, and/or speech therapy session.

**[0023]** Because γ-aminobutyric acid receptor agonists and 1,5-benzodiazepines, such as for example clobazam, have been used in clinical

situations, effective amounts for use herein may be determined by a physician. Thus, in the present invention, an "effective amount" of a γ-aminobutyric acid receptor agonist or 1,5-benzodiazepine, such as for example clobazam, is between about 1 mg/day to about 40 mg/day. More preferably, the effective amount is between about 10mg/day to about 20 mg/day. In the present invention, if clobazam is not used, the effective amount of the non-clobazam drug will be an amount sufficient to obtain the same clinical effect as clobazam at between about 1 mg/day to about 40 mg/day, preferably about 10 mg/day to about 20 mg/day.

**[0024]** As used herein, "long-acting" means that the γ-aminobutyric acid receptor agonists and 1,5-benzodiazepines, such as for example clobazam, of the present invention have half-lives that are at least about 12 hours to at least about 60 hours.

**[0025]** In another embodiment of the invention, there is provided a method for identifying a patient suffering from hemiparesis caused by a non-congenital hypertonia, which patient will benefit from treatment with a non-sedative, long-acting 1,5-benzodiazepine. This method comprises: (a) performing a first motor function test on a patient suffering from hemiparesis caused by a non-congenital hypertonia; (b) administering a fast-acting 1,5-benzodiazepine to the patient after completion of the first motor function test; (c) administering to the patient a second motor function test, which is identical to the first motor function test, while the patient is under the influence of the fast-acting 1,5-benzodiazepine; and (d) determining whether the patient's performance improved in the second motor function test compared to the first motor function test, wherein an improved performance in the second motor

function test is indicative that the patient will benefit from treatment with a non-sedative, long-acting 1,5-benzodiazepine.

**[0026]** In the present invention and particularly with respect to the foregoing embodiment, "fast-acting" means that the speed of onset of the 1,5-benzodiazepine, e.g., midazolam, is at least about 30-60 seconds when administered intravenously, which is a preferred route of administration. Typically, the plasma half-life of such a fast-acting drug is between about 2 to about 5 hours. The duration of a typical dose of such a fast-acting drug is between about 15 minutes and about 2 hours.

**[0027]** Midazolam has the chemical name 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a] [1,4]benzodiazepine. Midazolam is commercially available (from, e.g., Bedford Laboratories (Bedford, OH) as Midazolam HCl, 2 mg/2 ml) and is known by a number of tradenames, including, e.g., Dormicum, Midazolam Base, Midazolam HCl, Midazolamum, and Versed. Methods for the manufacture of midazolam are well known. See, e.g., U.S. Patent Nos. 4,440,685, 4,377,523, 6,262,260, and 6,512,114, which are incorporated by reference as if recited in full herein.

**[0028]** In the present invention, the fast-acting 1,5-benzodiazepine, e.g., midazolam, is preferably titrated to achieve, at most mild sedation (confirmed by no errors by the patient counting backward from 20 to 1). In another embodiment, the fast-acting 1,5-benzodiazepine is minimally sedative and preserves full awareness. More preferably, the fast-acting 1,5-benzodiazepine is non-sedative and is effective when administered orally.

**[0029]** In the present invention, when a range is stated for a particular parameter, *e.g.*, an effective amount, all values within that range, including the endpoints, are intended to be included.

**[0030]** In addition to the foregoing, effective dosage forms, modes of administration, and dosage amounts of the γ-aminobutyric acid receptor agonist and/or 1,5-benzodiazepine, *e.g.* clobazam or midazolam, respectively, may be determined empirically, and making such determinations is within the skill of the art in view of the disclosure herein. It is understood by those skilled in the art that the dosage amount will vary with the route of administration, the rate of excretion, the duration of the treatment, the identity of any other drugs being administered, the age, size, and species of mammal, and like factors well known in the arts of medicine and veterinary medicine. In general, a suitable dose of a γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, according to the invention will be that amount of such a compound or composition that is the lowest dose effective to produce the desired effect. The effective dose of the γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, may be administered as one, two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

**[0031]** The γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, of the present invention may be administered in any desired and effective manner: as pharmaceutical compositions for oral ingestion, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous,

topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. In the present invention, a preferred route of administration is oral. Further, the γ-aminobutyric acid receptor agonist or 1,5-benzodiazepine, *e.g.* clobazam of the present invention may be administered in conjunction with other treatments. The γ-aminobutyric acid receptor agonist or 1,5-benzodiazepine, *e.g.* clobazam may be encapsulated or otherwise protected against gastric or other secretions, if desired.

**[0032]** While it is possible for the γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, to be administered alone, it is preferable to administer such combination as a pharmaceutical formulation (composition). Pharmaceutically acceptable compositions of the invention comprise one or more γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, as active ingredients in admixture with one or more pharmaceutically-acceptable carriers and, optionally, one or more other compounds, drugs, ingredients and/or materials. Regardless of the route of administration selected, the γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, of the present invention may be formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art. *See, e.g.*, Remington 's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

**[0033]** Pharmaceutically acceptable carriers are well known in the art (*see, e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.))

and include sugars (*e.g.*, lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (*e.g.*, dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous solutions (*e.g.*, saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (*e.g.*, ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (*e.g.*, glycerol, propylene glycol, and polyethylene glycol), organic esters (*e.g.*, ethyl oleate and tryglycerides), biodegradable polymers (*e.g.*, polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, oils (*e.g.*, corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (*e.g.*, suppository waxes), paraffins, silicones, talc, silicylate, *etc.* Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

**[0034]** The pharmaceutical compositions of the invention may, optionally, contain additional ingredients and/or materials commonly used in pharmaceutical compositions. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate,

cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monosterate; (8) adsorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide, aluminum hydroxide, calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monosterate, gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride;

(26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and preservative agents. Each such ingredient or material must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Ingredients and materials suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable ingredients and materials for a chosen dosage form and method of administration may be determined using ordinary skill in the art.

**[0035]** Pharmaceutical compositions suitable for oral administration may be in the form of capsules, cachets, pills, tablets, powders, granules, a solution or a suspension in an aqueous or non-aqueous liquid, an oil-in-water or water-in-oil liquid emulsion, an elixir or syrup, a pastille, a bolus, an electuary or a paste. These formulations may be prepared by methods known in the art, *e.g.*, by means of conventional pan-coating, mixing, granulation or lyophilization processes.

**[0036]** Solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like) may be prepared by mixing the active ingredient(s) with one or more pharmaceutically-acceptable carriers and, optionally, one or more fillers, extenders, binders, humectants, disintegrating agents, solution retarding agents, absorption accelerators, wetting agents, absorbents, lubricants, and/or coloring agents. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using a suitable excipient. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using a suitable binder, lubricant, inert diluent, preservative, disintegrant, surface-active, or dispersing agent. Molded

tablets may be made by molding in a suitable machine. The tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein. They may be sterilized by, for example, filtration through a bacteria-retaining filter. These compositions may also optionally contain opacifying agents and may be of a composition such that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. The active ingredient can also be in microencapsulated form. Preferably, solid dosage forms of, e.g., clobazam may be purchased commercially in, e.g., 10 mg dosage forms (e.g., Frisium® Tablets, 10 mg sold by Aventis Pharma Ltd.).

**[0037]** Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. The liquid dosage forms may contain suitable inert diluents commonly used in the art. Besides inert diluents, the oral compositions may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents. Suspensions may contain suspending agents.

**[0038]** Pharmaceutical compositions for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more active ingredient(s) with one or more suitable nonirritating carriers which are solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active γ-aminobutyric acid receptor agonist or 1,5-

benzodiazepine, *e.g.* clobazam. Pharmaceutical compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such pharmaceutically-acceptable carriers as are known in the art to be appropriate.

**[0039]** Pharmaceutical compositions suitable for parenteral administrations comprise the γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, along with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain suitable antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient, or suspending or thickening agents. Proper fluidity can be maintained, for example, by the use of coating materials, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These compositions may also contain suitable adjuvants, such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption.

**[0040]** In some cases, in order to prolong the effect of a drug, it is desirable to slow its absorption from subcutaneous or intramuscular injection. In the present invention, it may be desirable to slow the absorbance of one, or more, or all of the actives. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility.

**[0041]** The rate of absorption of the drug(s) then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug(s) may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms may be made by forming microencapsule matrices of the active ingredient(s) in biodegradable polymers. Depending on the ratio of the active ingredient(s) to polymer, and the nature of the particular polymer employed, the rate of active ingredient release can be controlled. Depot injectable formulations are also prepared by entrapping the drug(s) in liposomes or microemulsions which are compatible with body tissue. The injectable materials can be sterilized for example, by filtration through a bacterial-retaining filter.

**[0042]** The γ-aminobutyric acid receptor agonist or a long- or fast-acting 1,5-benzodiazepine, *e.g.* clobazam and midazolam, respectively, of the present invention may be presented in unit-dose or multi-dose sealed containers, for example, ampules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

**[0043]** The following examples are provided to further illustrate the methods and compositions of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

## EXAMPLES

### EXAMPLE 1 - DIAGNOSTIC EFFICACY TESTING

**[0044]** A patient is monitored during the diagnostic evaluation by an experienced physician, including periodic blood pressure measurements and ECG and continuous pulse oximetry.

**[0045]** A baseline neurological exam, i.e., motor function test, is administered to the patient, including characterization of degree of weakness, degree and type of hypertonia in upper and lower extremities or in the articulatory speech apparatus. Sustained attention (ability to count backwards from 20 to 1 without error) is also tested at baseline. For hypertonia, distinction is made between *spasticity* (velocity-dependent increased tone on passive movement only) and *dystonia* (movement-dependent increased tone/co-contractions in antagonist muscle groups, or the production of a torsional movement on attempted movement that disrupts the targeted movement). A standardized scale of hypertonia, such as for example, the Ashworth scale is used to quantify degree of hypertonia on passive movement. A standardized scale of motor function, such as for example, the Fugl-Meyr scale is used to characterize motor function when the limb is involved. Standard tests of the dysarthria exam are used to characterize articulatory hypertonia. A standardized scale of strength, such as for example, the MRC 5-point motor scale or motor components of the NIH Stroke Scale (NIHSS) is used to characterize limb strength.

**[0046]** Midazolam is administered to patients as intravenous boluses, beginning with 1-mg (up to a maximum of 4 mg), titrated in 0.5-mg aliquots to mild sedation as measured by the inability to count backward from 20 to 1 without error. The administration of midazolam occurs over 10 to 15 minutes total, with the aliquots

being given every 2 to 5 minutes under close and repeated neurological exams for sustained attention.

**[0047]** The on-drug neurological exam for motor function (motor function test) and hypertonia is assessed within 2 minutes of establishment of mild sedation as characterized above. Videotaping is done for later adjudication and confirmation of the effect of the midazolam. Particular attention is placed on changes in movement of the hypertonic limb or speech, including (a) reduction of a dystonic component in showing less of a torsional component on movement of an affected limb; (b) greater excursion of a limb across any joint after administration of the midazolam compared to the baseline exam; (c) any functional improvement of an affected limb including more normal grasping or releasing at the hand, or more normal flexion or extension at the ankle, knee or hip, or change on the Fugl-Meyer scale; (d) reduction in tone with passive movement of a limb as measured by the Ashworth scale; (e) change in strength as measured by the MRC or motor component of the NIHSS; and (f) improved phonation on dysarthria exam. Thus, performance is evaluated in the second motor function test (on drug) compared to the first motor function test (off drug).

**EXAMPLE 2 - TREATMENT PROTOCOL**

**[0048]** Patients who demonstrate improvement with administration of the midazolam (i.e., in the second motor function test compared to the first motor function test) as outlined in Example 1, including reduction in hypertonia, increased excursion across a joint of an affected limb, or any other functional or strength improvement, or improvement in speech, is given oral clobazam for extended treatment of post-stroke dystonic hemiparesis.

**[0049]** The treatment regimen includes oral administration of clobazam, beginning with 5-mg po qd and tapering up as tolerated. The recommended titration of clobazam is as follows: begin 5 mg po qd for 1 week. Then, 5 mg po bid for 2 weeks. Then, 10 mg po qam, 5 mg po qpm for 2 weeks. Then, 10 mg po bid. Further titration up to 40 mg per day as tolerated and as continued improvements are documented.

**[0050]** Concurrent with initiating the oral clobazam, the patient participates in a routine of physical therapy (PT), occupational therapy (OT), speech therapy (ST), or combinations thereof focused on improving function of the affected limb(s) or speech. The PT/OT/ST routine occurs at a frequency of at least 3 times per week in 1 to 3 hour sessions, for 6 to 8 weeks.

**[0051]** Titration of the clobazam dose will depend on tolerability of the sedative effects in each patient. If sedation impedes normal functioning during the day, alternative dosing regimens include: (a) continuing at an intermediate dose or reducing the daily dose; or (b) administering the dose in the evening only, and undergoing physical and occupational therapy in the morning hours.

**[0052]** Assessment of functional improvements during treatment with clobazam and PT/OT take place during the course of therapy and after 2-3 months on the medication. If needed, discontinuation of the clobazam takes place with a taper over 2-4 weeks. Subsequent motor function assessments of patients who have come off clobazam may be conducted after 1-3 months as patients appear to attain lasting post-treatment effects, particularly in gait.

## EXAMPLE 3 - CLINICAL CASE

**[0053]** In one clinical case, the patient was a 37 year old right-handed woman with a right internal carotid artery dissection and right-middle cerebral artery stroke in 1995 with cortical and subcortical involvement. The patient suffered from left hemiparesis and developed hypertonia within a few weeks after the hemiparesis. The patient displayed an inability to open her hand or extend her wrist, an inability to dorsiflex at the left ankle, and attempts to achieve these movements produced increased tone and tremor.

**[0054]** The patient underwent the diagnostic efficacy testing as described in Example 1 with midazolam challenge in January, 2001. The on-drug examination revealed movement in the left foot of the patient for the first time in 6 years.

**[0055]** The patient was initially treated with Botox injections and oral baclofen. No functional improvement was observed with these treatments.

**[0056]** In February 2003, the treatment protocol as described in Example 2 with clobazam was initiated, which replicated the results of the midazolam challenge, but without sedation. In combination with physical and occupational therapy, the patient obtained functional improvement in hand and foot movement and improvement in gait.

**[0057]** To date, seven other patients suffering from similar disorders have been treated according to the protocols set forth in Examples 1 and 2 and results similar to those described in Example 3 have been obtained. Table 2 below summaries the patients administered the protocol disclosed in Examples 1 and 2.

**Table 2 – Treated Patients**

| Pt no. | Age/gender | Stroke location | Syndrome | Time to midazolam |
|---|---|---|---|---|
| 1 | 34/F | R basal ganglia | Left hemiparesis | 6 years |
| 2 | 37/F | Left basal ganglia, L insula | R hemiparesis, aphasia | 13 years |
| 3 | 84/M | Left basal ganglia, L insula | R hemiparesis, aphasia | 5 yrs |
| 4 | 79/M | R int caps, basal gang, CR | L hemiparesis | 11 years |
| 5 | /F | | | Stroke 2000 |
| 6 | 77/M | L thalamus, L medulla | R hemiparesis | 4 years |
| 7 | 83/F | R frontal, parietal | L hemipaersis, L neglect | 6 months |
| 8 | 69/M | L thalamus, basal gang, CR (hematoma) | R hemiparesis | 6 months |

**[0058]** Although illustrative embodiments of the present invention have been described herein, it should be understood that the invention is not limited to those described, and that various other changes or modifications may be made by one skilled in the art without departing from the scope or spirit of the invention.

**What is claimed is:**

1. A method for treating or ameliorating the effects of a non-congenital hypertonia in a patient comprising administering to the patient an effective amount of a non-sedative, long-acting γ-aminobutyric acid receptor subtype A ($GABA_A$) agonist or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

2. The method according to claim 1, wherein the $GABA_A$ agonist is a 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

3. The method according to claim 2, wherein the 1,5-benzodiazepine is clobazam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

4. The method according to any one of claims 1, 2, or 3, wherein the effective amount is between about 1 mg/day to about 40 mg/day.

5. The method according to claim 4, wherein the effective amount is between about 10 mg/day to about 20 mg/day.

6. The method according to any one of claims 1, 2, or 3 further comprising treating the patient with a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof.

7. The method according to claim 6, wherein through the sustained action of the $GABA_A$ agonist the effect of the routine is carried over to the patient's personal environment.

8. The method according to claim 1, wherein the non-congenital hypertonia is characterized by a symptom selected from the group consisting of dystonia, spasticity, and combinations thereof.

9. The method according to claim 1, wherein the non-congenital hypertonia is caused by a central nervous system disease or injury.

10. The method according to claim 9, wherein the central nervous system disease or injury is selected from the group consisting of stroke, head trauma, brain tumor, post-surgical injury, cerebral palsy, and primary and secondary dystonias.

11. The method according to claim 10, wherein the central nervous system disease or injury is a stroke.

12. A pharmaceutical composition for treating or ameliorating the effects of a non-congenital hypertonia in a patient comprising a pharmaceutically acceptable carrier and an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

13. The pharmaceutical composition according to claim 12, wherein the non-sedative, long-acting 1,5-benzodiazepine is clobazam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

14. The pharmaceutical composition according to any one of claims 12 or 13, which is in an unit oral dosage form of about 10 mg to about 20 mg.

15. A method for rehabilitating hemiparesis caused by post-stroke hypertonia comprising:

a. administering to a patient suffering from hemiparesis caused by post-stroke hypertonia an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof; and

b. treating the patient with a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

16. The method according to claim 15, wherein through the sustained action of the 1,5-benzodiazepine the effect of the routine is carried over to the patient's personal environment.

17. The method according to claim 15, wherein the non-sedative, long-acting 1,5-benzodiazepine is clobazam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

18. The method according to any one of claims 15 or 17, wherein the effective amount is between about 1 mg/day to about 40 mg/day.

19. The method according to claim 18, wherein the effective amount is between about 10 mg/day to about 20 mg/day.

20. A system for improving the clinical outcome of a patient suffering from hemiparesis caused by a non-congenital hypertonia comprising:

a. prescribing, administering, or causing to be administered to a patient suffering from hemiparesis caused by a non-congenital hypertonia an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof; and

b. further prescribing, administering, or causing to be administered to the patient a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

21. The system according to claim 20, wherein through the sustained action of the 1,5-benzodiazepine the effect of the routine is carried over to the patient's personal environment.

22. A method for identifying a patient suffering from hemiparesis caused by a non-congenital hypertonia, which patient will benefit from treatment with a non-sedative, long-acting 1,5-benzodiazepine comprising:

a. performing a first motor function test on a patient suffering from hemiparesis caused by a non-congenital hypertonia;

b. administering a fast-acting 1,5-benzodiazepine to the patient after completion of the first motor function test;

c. administering to the patient a second motor function test, which is identical to the first motor function test, while the patient is under the influence of the fast-acting 1,5-benzodiazepine; and

d. determining whether the patient's performance improved in the second motor function test compared to the first motor function test, wherein an improved performance in the second motor function test is indicative that the patient will benefit from treatment with a non-sedative, long-acting 1,5-benzodiazepine.

23. The method according to claim 22, wherein the first and second motor function tests comprise evaluating the patient's tone, power, flexion, and extension at a joint.

24. The method according to claim 22, wherein the improved performance in the second motor function test compared to the first motor test is selected from the group consisting of improved tone, improved power, improved flexion, and improved extension at a joint, and combinations thereof.

25. The method according to claim 22, wherein the fast-acting 1,5-benzodiazepine comprises midazolam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

26. The method according to claim 22, wherein the fast-acting 1,5-benzodiazepine is administered in a dose that is minimally sedative and preserves full awareness.

27. The method according to claim 22, wherein the fast-acting 1,5-benzodiazepine is non-sedative.

28. The method according to claim 23, wherein the joint is selected from the group consisting of a wrist, an elbow, a knee, an ankle, and combinations thereof.

29. The method according to claim 28, wherein the joint is a wrist and an ankle.

30. The method according to claim 22 further comprising administering to those patients identified in step (d) an effective amount of a non-sedative, long-acting 1,5-benzodiazepine or precursors, analogs, enantiomers, optical isomers, diastereomers, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

31. The method according to claim 30, wherein the non-sedative, long-acting 1,5-benzodiazepine is clobazam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof.

32. The method according to any one of claims 30 or 31, wherein the effective amount is between about 1 mg/day to about 40 mg/day.

33. The method according to claim 32, wherein the effective amount is between about 10 mg/day to about 20 mg/day.

34. The method according to claim 30 further comprising treating the patient with a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

35. The method according to claim 34, wherein through the sustained action of the non-sedative, long-acting 1,5-benzodiazepine the effect of the routine is carried over to the patient's personal environment.

36. The method according to claim 22, wherein the non-congenital hypertonia is characterized by a symptom selected from the group consisting of dystonia, spasticity, and combinations thereof.

37. The method according to claim 22, wherein the non-congenital hypertonia is caused by a central nervous system disease or injury.

38. The method according to claim 37, wherein the central nervous system disease or injury is selected from the group consisting of stroke, head trauma, brain tumor, post-surgical injury, cerebral palsy, and primary and secondary dystonias.

39. The method according to claim 38, wherein the central nervous system disease or injury is a stroke.

40. The method according to any one of claims 22 or 34, wherein the benefit is selected from the group consisting of improved tone, improved power, improved flexion, improved extension at a joint, improved muscle control, improved gait, improved speech, improved motor control, improved coordination, and combinations thereof.

41. A method for rehabilitating hemiparesis caused by post-stroke hypertonia comprising:

a. prescribing, administering, or causing to be administered to a patient suffering from hemiparesis caused by post-stroke hypertonia between about 10 mg/day to about 20 mg/day of clobazam or precursors, analogs, N-oxides, crystalline forms, hydrates, metabolites, or pharmaceutically acceptable salts thereof; and

b. prescribing, administering, or causing to be administered to the patient a routine selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof, which routine is targeted to rehabilitating the hemiparesis.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/05274

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/62; A61K 31/55 (2008.04)
USPC - 514/221
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/371 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
US WEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Dialog PRO (Engineering)
1,5-benzodiazepin$, non-congenital hypertonia, dystonia, stroke, head trauma, cerebral palsy, brain tumor, clobazam.midalozam, hemiparesis, rehabilitation, occupational therapy, physical therapy, speech therapy, motor function test.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>-----<br>Y | US 2007/0043038 A1 (STARCK et al.) 22 February 2007 (22.02.2007) para [0288], [0292], [0310], [0315], [0325]-[0328] | 1-5, 8-14<br>----------<br>6-7, 15-21, 30-41 |
| Y | US 2006/0194677 A1 (WHITALL et al.) 31 August 2006 (31.08.2006) para [0089]-[0091], [0093] | 6-7, 15-41 |
| Y | US 2004/0225335 A1 (WHITEHURST et al.) 11 November 2004 (11.11.2004) para [0105] | 22-40 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 09 July 2008 (09.07.2008) | 17 JUL 2008 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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